临床研究

21-三体综合征相关急性白血病21例报告

冉云霓,于 洁,宪 莹,温贤浩,郭玉霞,管贤敏,肖剑文
重庆医科大学附属儿童医院,重庆 400014

摘要:目的 总结21-三体综合征(DS)相关急性白血病(AL)患儿的临床、实验室检查特点及疗效,提高诊疗水平。**方法** 分析21例DS-AL患儿的临床表现、实验室检查、治疗及预后。**结果** 与非DS-AL相比,21例DS-AL患儿发病年龄1~5岁为主(占85.7%),急性髓细胞白血病多见(占57.1%),乳酸脱氢酶>2倍以上者较多(占61.9%);13例行心脏彩超检查10例异常(占67.9%),复杂型先天性心脏病常见(占38.5%);6例接受化疗,4例完全缓解(占66.7%),合并感染死亡2例,治疗相关死亡率33.3%;2例减强度化疗者已分别无病生存21月及43月。**结论** DS-AL以急性髓细胞白血病多见,对化疗敏感,采用减强度化疗预后较好。
关键词:21-三体综合征;急性白血病;临床分析;减强度化疗

Acute leukemia associated with Down syndrome: clinical analysis of 21 cases

RAN Yunni, YU Jie, XIAN Ying, WEN Xianhao, GUO Yuxia, GUAN Xianmin, XIAO Jianwen
Children's Hospital of Chongqing, Chongqing Medical University, Chongqing, 400014

Abstract: Objective To summarize the clinical characteristics, laboratory findings and prognosis of patients with Down syndrome-related acute leukemia (DS-AL). **Methods** The clinical data, laboratory findings, chemotherapy and prognosis of 21 children with DS-AL were analyzed. **Results** Most of the children had disease onset of leukemia at 1 to 5 years of age (85.7%), and acute myeloid leukemia accounted for 57.1% of these cases; 61.9% of the patients had increased lactate dehydrogenase level by 2 folds or more. Of the 13 cases undergoing echocardiography, 10 (67.9%) showed abnormal findings, and complex congenital heart disease was common (38.5%). Six of the children received chemotherapy and complete remission was achieved in 4 cases; 2 patients died of infection, and the treatment-related mortality was 33.3%. The 2 patients receiving reduced intensive chemotherapy have so far had event-free survival for 21 and 43 months. **Conclusion** Acute myeloid leukemia is the most common subtype of DS-AL. Patients with DS-AL are sensitive to chemotherapy and the prognosis was favorable with reduced intensive chemotherapy.
Key words: Down syndrome; acute leukemia; clinical analysis; reduced intensive chemotherapy

21-三体综合征(Down syndrome, DS)是最常见的染色体病。DS发生急性白血病(acute leukemia, AL)等在内的血液系统疾病风险显著高于非DS人群,继发于DS的AL(DS-AL)患儿临床表现、实验室检查、治疗及预后与非DS-AL有很大差异,采用恰当治疗,DS-AL疗效高于非DS-AL[1]。目前国内缺乏DS-AL较大样本报道,对中国人群疾病特点缺乏了解;由于存在误区,接受治疗的DS-AL也甚为少见。为提高DS-AL诊疗水平,收集2004年8月~2014年8月本院诊治21例DS-AL患儿的临床资料、实验室检查及治疗情况,报道如下。

1 资料和方法

1.1 一般资料

2004.08.01~2014.08.01本院收治DS-AL患儿21例,男8例,女13例。年龄4 d到11岁3月(平均年龄3.15岁,中位年龄1岁6月),0~1岁组1例,1~5岁组17例,>5岁组3例。所有患儿均有眼距宽、眼裂小、外眼角上斜、鼻梁低平等特殊面容及通贯掌、草履足等皮纹改变。发病时有发热8例,出血15例(均为皮肤出血)、肝脾肿大16例(仅肝脏肿大3例,仅脾脏肿大1例,肝脾均肿大12例)、骨痛及黄疸各1例,所有患儿均无睾丸及中枢神经系统浸润表现。

1.2 检查

初诊血常规(表1):白细胞(WBC)2.4~122.0×10^9/L(平均值28.39±34.17×10^9/L,中位值9.67×10^9/L),15例外周血可见幼稚细胞;血小板(PLT)4~77×10^9/L(平均值21.67±16.91×10^9/L,中位数14×10^9/L);血红蛋白(Hb)32~145g/L(平均值74.05±28.87 g/L,中位数74 g/L)。

骨髓检查:骨髓细胞学及组织化学染色、结合流式细胞术免疫分型后按FAB分型(表2):急性淋巴细胞白血病(ALL)6例,急性髓细胞性白血病(AML)12例,3例为形态学不能分型结合流式细胞术确诊为急性混合细胞性白血病(MAL)。16例做骨髓染色体核型:12例仅

收稿日期:2015-10-21
作者简介:冉云霓,硕士,住院医师,E-mail: ran.rainy@qq.com
通信作者:肖剑文,本科,副主任医师,E-mail: tomahawk60@sohu.com

表1 初诊血常规

Tab.1 Findings in routine blood tests at diagnosis

	Hb (g/L)				WBC count (×10⁹/L)			PLT count (×10⁹/L)	
	>110	90-110	60-90	30-60	>4	4-10	<10	<50	<20
Cases (*n*)	2	3	7	9	3	8	10	9	12
Ratio	9.5%	14.3%	33.3%	42.9%	14.3%	38.1%	47.6%	42.9%	57.1%

有21三体;4例AML合并其它核型异常,分别为:①49,XX, der(3)t(1;3) (q32;q22.9), del(6) (q13;q21), +8, +21,+11;②48,XX,-C, +2G/47,XX,+G;③49,XX,add(9)(p22)x2,+11,der(11;14)(q10;q10),+20,der(20;22)(q10;q10),+21(15)/47,XX,+21(5);④48,XY,+10,+21/46,XY。10例做白血病融合基因检测均未见异常。

14例患儿行外周血染色体核型分析确诊DS(4例系家属口述,未见报告),7例骨髓染色体检查结合临床

表2 细胞学及免疫分型与发病年龄

Tab.2 Age at diagnosis and cytological and immunological phenotypes of the patients

Age, morphology and immunophenotype		<1yr (*n*)	1-5yr (*n*)	>5yr (*n*)	Total (*n*, %)
ALL	ALL-L1	0	0	1	6(28.6%)
	ALL-L2	1	2	2	
AML	AML-M1	0	2	0	12 (57.1%)
	AML-M2a	0	5	0	
	AML-M5a	0	2	0	
	AML-M5b	0	1	0	
	AML-M7	0	2	0	
MAL	AML+pre-B-ALL	0	2	0	3 (14.3%)
	C-B-ALL+AML	0	1	0	
	Total (*n*, %)	1 (4.7%)	17 (81.0%)	3 (14.3%)	21 (100%)

表现确诊DS。可供分析的外周血染色体报告10例均为标准型。

肝功检查有1例胆红素增加,5例谷丙转氨酶增加,18例有乳酸脱氢酶(LDH)增加(262-5050 U/L,平均值1092.22±1072.11 U/L、中位值849 U/L,参考值110~330 U/L)。

13例行心脏彩超检查,10例有先天性心脏病。包括单纯室间隔缺损(ventricular septal defect, VSD)2例、房间隔缺损(atrial septal defect, ASD)1例及卵圆孔未闭2例;5例有2种及以上先天性心脏病,包括3例VSD合并动脉导管未闭(patent ductus arteriosus, PDA),1例ASD合并PDA,1例ASD、VSD、PDA合并主动脉缩窄。

1.3 治疗

6例患儿接受至少一个疗程化疗(4例AML,1例ALL,1例MAL)。2例AML患儿接受DAE方案化疗达到完全缓解(complete remission, CR)未继续治疗,失访;AML及ALL各1例分别给予DAE、VDLP方案化疗,因明显骨髓抑制合并严重感染死亡;AML和MAL各1例接受减强度规范化疗达到持续CR,分别无病生存21月及43月[2]。

2 结果

本组患儿均有DS典型面容且及皮纹改变,结合染色体检查确诊DS,骨髓检查均确诊为AL。男女性别比0.615∶1,女性多见。AL以发热、贫血、出血及浸润为主要表现,无睾丸及中枢神经系统浸润;发病年龄1-5岁组为主,占85.7%(表2)。

所有患儿均血小板减少,PLT<20×10⁹/L为主,占57.1%。19例有贫血,占90.5%,9例为重度贫血,占42.9%。白细胞计数异常者为主,其中白细胞降低3例、增高10例、正常者8例,分别占14.3%、47.6%及38.1%;15例外周血可见异常细胞,占71.4%(表1)。

骨髓检查6例ALL(占28.6%),12例AML(占

57.1%),3例MAL(占14.3%),AML多见。AML以AML-M2a型为主,占41.7%。1例AML-M2a型系骨髓异常增生综合征(myelodysplastic syndrome,MDS)转化。ALL发病时<1岁1例,1~5岁2例,>5岁3例,AML及MAL发病年龄均1~5岁(表2)。除21-三体外骨髓染色体有其它异常者均为AML且系复杂核型。白血病融合基因检查均未见异常。

21例患儿有18例LDH增加,占85.7%,其中>2倍以上16例(占61.9%)。13例行心脏彩超检查10例异常者(占67.9%),以复杂型先天性心脏病为主(占38.5%)。

接受化疗的6例患儿有4例CR(占66.7%),2例因骨髓抑制合并严重感染死亡,治疗相关死亡率(treat-related mortality, TRM)33.3%。2例接受减强度规范治疗持续CR。

3 讨论

DS系出生时21-染色体为三体所致,是最常见的染色体病,以典型的特殊面容和认知损害、高发心脏及免疫缺陷等先天畸形为特征[1]。本组患儿均有DS典型面容且及皮纹改变,结合染色体检查确诊为DS,骨髓检查确诊AL,本组患儿均DS-AL诊断明确。

研究发现[3]DS患儿容易发生多种血液系统疾病如巨红细胞症、短暂性血小板计数异常、暂时性骨髓增殖性疾病、MDS等。国外资料表明[4]DS-AL发病率2.7%,为非DS儿童14~30倍。非DS-AL患儿以ALL为主,而DS-AL则以AML常见,本组病例AML者12例,ALL者6例,符合DS-AL发病特征。目前国内没有DS-AL发病率的资料。

文献报道[5]无论DS或非DS人群,AL发病均以发热、贫血、出血、肝脾肿大等浸润为主要表现,血常规多表现为血小板及血红蛋白减少,白细胞计数增高及外周血发现异常细胞多见,与本组病例一致。有报道建议DS患儿可考虑定期骨髓检查争取早期发现AL[3],但何时及何种情况下骨髓检查尚无结论。LDH增高可能与肿瘤性疾病相关,本组患儿LDH多大于正常值2倍以上,故LDH增加可考虑作为DS行骨髓检查的指征。文献报道DS合并MDS机会较高[6],本组患儿仅1例患儿有MDS病史,可能与样本量较少有关,也提示怀疑合并血液系统疾病拟行骨髓检查时应同时做骨髓活检。本组患儿中可供分析的外周血染色体报告10例均为标准型,提示标准型DS发生AL的可能性较大。

DS-AML发病率为非DS-AML的150倍[7]。由于DS-AML有其独特的生物学和临床特征,故WHO-2008分类系统将其定义为一种独特的AML亚类[5],其临床特点包括[8]:诊断时年龄一般≤5岁、多无中枢神经系统浸润证据、既往多有MDS病史等,与本组患儿特征一致。本组患儿以女性居多,白细胞计数增高多见,细胞形态学分型AML-M2a最多,但文献报道DS-AML无明显性别差异、白细胞计数较低、FAB分型多为M7和未分型AML[9-10],考虑与本组样本量小有关。

DS-ALL占DS-AL约1/3,发病率为非DS-ALL的10~20倍[1]。与DS-AML相比,DS-ALL多发生于1~10岁,婴儿白血病少见[8]。本组DS-ALL年龄也无明显特点,表明与非DS组相比,DS-ALL临床表现特异性不显著[3]。

21-三体染色体对阿糖胞苷等药物代谢有影响且DS-AL白血病细胞多存在GATA1突变,故DS-AL患儿对多种化疗药物尤其是阿糖胞苷、甲氨蝶呤及蒽环类敏感[12-13],DS-AL积极治疗预后较好。但药物副作用尤其是严重骨髓抑制常增加感染机会,而DS多合并先天性心脏病,故患儿多不能耐受高强度化疗。高强度化疗相关死亡是DS-AL预后不良的主要因素[14],本组接受治疗的6例患儿中4例系采用标准化疗方案,2例因严重感染死亡。目前DS-AL多采用减强度的化疗方案[15],降低治疗相关死亡率而不影响无病生存率。尤其是DS-AML的预后明显好于非DS(4年无病生存率分别为88%和42%,P<0.001)[9-10]。也有研究表明[16],与标危化疗方案相比,DS-ALL患儿接受高危化疗方案后预后更好,通过积极处理强化治疗相关的不良反应和改善支持治疗,可将DS-ALL患儿的EFS提高到接近80%,与非DS持平。本组2例患儿(AML和MAL各1例)经减强度化疗均达到CR,治疗相关副作用轻微,均无病生存[2],表明采用恰当的治疗,DS-AL预后良好。

由于认识不足,国内仅有DS-AL个案报道,更缺乏疗效及预后相关资料,本文首次较大样本报道DS-AL尤其是治疗、预后。发现DS-AL尤其是DS-AML与非DS-AL临床特点、治疗方案及疗效均存在一定差异,应积极鼓励DS-AL尤其是DS-AML患儿接受以减低强度为主的化疗。

参考文献:

[1] Pikora TJ, Bourke J, Bathgate K, et al. Health conditions and their impact among adolescents and young adults with Down syndrome[J]. PLOS One, 2014, 9(5): e96868.

[2] 冉云霓, 于 洁, 宪 莹, 等.减低强度化疗治疗儿童21-三体综合征合并急性白血病二例并文献复习[J]. 中华血液学杂志, 2014, 35(12): 1119-21.

[3] Manivannan P, Prasaad PR, Kar R, et al. Down syndrome with different hematological manifestations: a short series of 3 cases with review of literature[J]. Indian J Hematol Blood Transfus, 2013, 29(1): 31-4.

[4] Maloney KW, Taub JW, Ravindranath Y, et al. Down syndrome preleukemia and leukemia[J]. Pediatr Clin North Am, 2015, 62(1): 121-37.

[5] Davis KL, Marina N, Arber DA, et al. Pediatric acute myeloid leukemia as classified using 2008 WHO criteria: a single-center experience[J]. Am J Clin Pathol, 2013, 139(6): 818-25.

[6] Lam GK, Leung AW, Ha SY, et al. Acute leukemia in down syndrome children in Hong Kong: retrospective review[J]. J Pediatr Hematol Oncol, 2016, 38(2): 102-6.
[7] Khan I, Malinge S, Crispino J. Myeloid leukemia in Down syndrome [J]. Crit Rev Oncog, 2011, 16(1/2): 25-36.
[8] Arico M, Ziino O, Valsecchi MG, et al. Acute lymphoblastic leukemia and Down syndrome: presenting features and treatment outcome in the experience of the Italian Association of Pediatric Hematology and Oncology (AIEOP) [J]. Cancer, 2008, 113(3): 515-21.
[9] Lange BJ, Kobrinsky N, Barnard DR, et al. Distinctive demography, biology, and outcome of acute myeloid leukemia and myelo-dysplastic syndrome in children with Down syndrome: children's cancer group studies 2861 and 2891[J]. Blood, 1998, 91(2): 608-15.
[10] Li MJ, Lee NC, Yang YL, et al. Long-term outcome for Down syndrome patients with hematopoietic disorders[J]. J Form Med Assoc, 2016, 115(2): 94-9.
[11] Tigay JH. A comparison of acute lymphoblastic leukemia in Down syndrome and non-Down syndrome children: the role of trisomy 21 [J]. J Pediatr Oncol Nurs, 2009, 26(6): 362-8.
[12] Ono R, Hasegawa D, Hirabayashi S, et al. Acute megakaryoblastic leukemia with acquired trisomy 21 and GATA1 mutations in phenotypically normal children[J]. Eur J Pediatr, 2015, 174(4): 525-31.
[13] Hefti E, Blanco JG. Anthracycline-Related cardiotoxicity in patients with acute myeloid leukemia and down syndrome: a literature review[J]. Cardiovasc Toxicol, 2016, 16(1): 5-13.
[14] Malinge S, Izraeli S, Crispino JD. Insights into the manifestations, outcomes, and mechanisms of leukemogenesis in Down syndrome [J]. Blood, 2009, 113(12): 2619-28.
[15] Ravindranath Y, Chang M, Steuber CP, et al. Pediatric oncology group (POG) studies of acute myeloid leukemia (AML): a review of four consecutive childhood AML trials conducted between 1981 and 2000[J]. Leukemia, 2005, 19(12): 2101-16.
[16] O'rafferty C, Kelly J, Storey L, et al. Child and adolescent Down syndrome-associated leukaemia: the Irish experience[J]. Ir J Med Sci, 2015, 184(4): 877-82.

（编辑:经 媛）